

### **REMARKS**

Applicant respectfully requests reconsideration. Claims 1-15 were previously pending in this application.

By this amendment, Applicant is canceling claim 13 without prejudice or disclaimer. Claim 15 has been amended to advance prosecution. New claims 16-19 have been added. Support for the new claims may be found in the application as filed. Specifically, support for claim 16 may be found in claim 15 as filed. Support for claim 17 may be found on page 6, line 8. Support for claim 18 may be found on page 6, lines 6-10. Support for claim 19 may be found on page 6, line 32. No new matter has been added.

#### **Rejections under 35 U.S.C. §101**

Claim 13 was rejected under 35 U.S.C. 101. The Examiner alleges that claim 13 is directed to non-statutory subject matter. Without conceding to the merits of the Examiner's position, claim 13 has been canceled rendering this rejection moot.

#### **Rejections under 35 U.S.C. §112**

Claims 13 and 15 were rejected under 35 U.S.C. §112, first paragraph. The Examiner asserts that the specification while enabling a method of treating hypercytokinemia to the extent that there is shown an increased survival rate for an in vivo model treated with riboflavin as compared to the in vivo model not treated with riboflavin, does not reasonably provide enablement for the prevention of general hypercytokinemia nor for treatment without a specified endpoint.

Claim 13 has been canceled. Claim 15 has been amended to overcome this rejection. The term "preventing" has been deleted from claim 15 and "to increase the survival rate of the subject" has been specified as an endpoint. As currently amended, claim 15 is directed to a method for *treating* hypercytokinemia with riboflavin, a riboflavin derivative or a pharmacologically acceptable salt thereof to increase the survival rate of the subject.

In view of the above amendments withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 13 and 15 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Without conceding to the merits of the Examiner's position, claim 13 has been canceled rendering the rejection of claim 13 under 35 U.S.C. §112, second paragraph moot. The Examiner asserts that Claim 15 "fails to recite a specified end point for the treatment and it is not apparent from the claim step(s) which one set of steps would have resulted in "preventing" the disease state." Claim 15 has been amended by deleting the term "preventing" from the claim and by specifying increased survival rate as the endpoint of treatment.

In view of the above amendments withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph is respectfully requested.

#### Rejections Under 35 U.S.C. §103

Claims 13 and 15 were rejected under 35 U.S.C. §103(a) as being unpatentable over Araki et al. (US Patent No. 5,814,632) in view of Blomberg et al. (Post-transplant cytokine monitoring. ASHI Quaterly; First Quarter (2001)). The Examiner alleges that Araki et al. teach an immunopotentiating compound comprising riboflavin (and derivatives thereof) to treat infection. Araki et al. define immunopotentiating as enhancing the immune function. The Examiner asserts that Blomberg et al. teach that "an increase in cytokines (hypercytokinemia) is associated with organ transplants and monitoring of same is important for proper adjustments to immunosuppression following grafts and for graft acceptance (see col 2 first paragraph and col 3 last paragraph)." Based on the above teachings, the Examiner alleges that "one of ordinary skill in the art would have found it obvious that riboflavin is useful in organ transplants because it reduces the amount of cytokines released by the host; a necessary function of allograft acceptance as discussed in Blomberg et al."

Applicant respectfully traverses the rejection and requests that the Examiner reconsider the rejection for the following reasons. The Examiner has not made a *prima facie* case for rejecting the claims under §103. A *prima facie* case of obviousness requires some suggestion or motivation to modify/combine the teaching(s) of the reference(s) and have a reasonable

expectation of success in doing so. Regardless of whether one of ordinary skill in the art could have modified an art reference, the requirement for making an obviousness rejection is that the person of ordinary skill in the art have some motivation to make the modification. The suggestion or motivation to modify/combine the teachings may be found either in the reference(s) itself/themselves or in the knowledge generally available to one of ordinary skill in the art, (MPEP § 2143). Describing “the teaching or the motivation to combine is an essential evidentiary component of an obviousness holding.” *C. R. Bard Inc. v M3 Sys. Inc.* 157 F.3d 1340, 1352 (Fed. Cir. 1998).

The Examiner has not made out a *prima facie* case of obviousness, because the Examiner has not provided any description or supporting evidence of the motivation that the skilled person would have had in making the modifications to the cited references as suggested by the Examiner. This is elaborated in the following.

Araki et al. teach that riboflavins (riboflavin and derivatives thereof) are immunopotentiating compounds (i.e, compounds that enhance the immune function). However, Araki et al. do not address the relationship between immunopotentiating effects of riboflavins and cytokines.

Blomberg et al. teach that increased cytokines are important in driving immune responses towards more antibody production, T cell killing function, or T cell regulatory activity, depending whether the cytokines are of the T<sub>H</sub>1 or T<sub>H</sub>2 type. However, Blomberg et al. do not address the relationship between increased cytokines and riboflavins. Moreover, Blomberg et al. teach only that cytokine levels can be monitored as a way to decide the appropriate immunosuppression therapy to administer.

The teachings of Araki et al. and Blomberg et al. alone or in combination do not address the relation between cytokines and riboflavins or establish a link or relation between riboflavins and cytokines let alone a teaching or suggestion that riboflavins decrease cytokines as the Examiner asserts. Thus, neither Araki et al. nor Blomberg et al., alone or in combination, teach or suggest the claimed invention.

Moreover, based on the combined teachings of Araki et al. and Blomberg et al., one of ordinary skill in the art would expect, if anything, that riboflavins will increase certain cytokines (rather than decrease cytokines as asserted by the Examiner). This is so because Araki et al. teach

that riboflavins are immunopotentiating agents and Blomberg et al. teach that cytokines are involved in immunopotential (Blomberg et al. page 18, left column, 2<sup>nd</sup> paragraph). Those teachings suggest to one of ordinary skill in the art that one possible way by which riboflavins might potentiate the immune response would be by increasing cytokines or that riboflavin's immunopotentiating effect might be mediated via an increase in cytokines. The combined teachings of Araki et al. and Blomberg et al. certainly would not suggest that riboflavin decrease cytokines or that riboflavins may be used to treat hypercytokinemia (as claimed in the instant invention).

In summary, the teachings of Araki et al. and Blomberg et al. in combination do not teach or suggest the instant claims and in fact teach away from the instant claims.

Claims 13 and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble RF (Effect of antioxidative vitamins on immune function with clinical applications. Int J Vitam Nutr Res. (1997); 67(5):312-20). The Examiner alleges that Grimble teaches that "antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway." According to the Examiner, "one of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia." The Examiner concludes that Grimble "teaches and makes prima facie obvious how to use the claimed invention at the time that it was made."

Applicant respectfully disagrees with the Examiner. Grimble examined the effects of antioxidative vitamins on immune function. Grimble teaches that the antioxidative vitamins ascorbic acid and tocopherols are important in preventing increased cytokine production. However, contrary to the Examiner's assertion, Grimble does not teach or suggest that riboflavin prevents increased cytokine production. Grimble found that "[r]iboflavin is an important cofactor in glutathione metabolism because of its role as a cofactor for glutathione reductase. However, whether this role is responsible for the influence of the vitamin on immune function is unclear." (Grimble, page 317 left column, 2nd full paragraph). The only examples of the effects of a lack of riboflavin are: a decrease in lymphocytes, decreased thymus weight, and a decreased antibody response. Grimble does not report any effect of riboflavin on cytokines. Thus, Grimble does not teach or suggest any relationship between riboflavin and cytokines.

Therefore, Grimble does not teach, suggest or even provide the motivation for one of ordinary skill in the art to use riboflavin to reduce cytokines let alone a teaching or a suggestion to use riboflavin to treat hypercytokinemia.

Claims 13 and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble RF as applied to claims 13 and 15 above and further in view of Sammon (Dietary linoleic acid, immune inhibition and diseases. Postgrad Med J 1999; 75:129-132).

The Examiner re-states that “Grimble teaches that antioxidative vitamins such as riboflavin prevents increased cytokine production via the glutathione production pathway.” According to the Examiner, “one of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia.” The Examiner then concludes that Grimble “teaches and makes prima facie obvious how to use the claimed invention at the time that it was made.”

The Examiner also asserts that Sammon teaches that “a lack of riboflavin causes an increase in cytokine production by modulating the glutathione production pathway which in turn causes an increase in PGE2 and cytokine production.”

According to the Examiner, one of ordinary skill in the art would have been motivated to combine Grimble and Sammon and obtain the claimed invention. The Examiner finds the motivation to combine Grimble and Sammon in the fact that both are directed to riboflavin's effect on the glutathione production pathway and cytokine production. The Examiner alleges that Sammon and Grimble “compliment each other in that Grimble teaches the effects of riboflavin and Sammon supports Grimble by discuss[ing] the effects when there is a lack of riboflavin.” The Examiner concludes that the combination of Sammon and Grimble “teach and make prima facie obvious” the claimed invention.

Applicant disagrees and respectfully traverses the rejection for the following reason. Applicant's arguments presented above regarding the teachings of Grimble are reiterated and are applicable here. As explained above, Grimble does not teach or suggest that riboflavin prevents increased cytokine production.

The Examiner's interpretation of the teachings of Sammon is incorrect. Sammon teaches that “[h]igh intake of linoleic acid in a diet deficient in other polyunsaturated fatty acids and in

riboflavin results in high tissue production of prostaglandin E2 which in turn causes *inhibition* of the proliferation and cytokine production of Th1 cells, mediators of cellular immunity.”

(Emphasis added – See Sammon Abstract). Thus, the teachings of Sammon are contrary to what the Examiner is asserting namely, that “a lack of riboflavin causes an *increase* in cytokine production”. (Emphasis added).

The teaching of Sammon that a diet deficient in riboflavin causes an inhibition in cytokine production suggests to one of ordinary skill in the art that riboflavin might stimulate or increase cytokine production which is the opposite of what is required by the instant claims. Thus, Sammon teaches away from the instant claims.

In summary, the teachings of Grimble and Sammon alone or in combination do not teach or suggest the instant claims and in fact teach away from the instant claims.

In view of the above arguments, withdrawal of the rejection of the claims under 35 U.S.C. §103, is respectfully requested.

#### Double Patenting Rejection

The Examiner provisionally rejected claims 13 and 15 under the judicially created doctrine of obviousness-type double patenting over claim 1-20 of co-pending US application 10/472621. Without conceding to the merits of the Examiner’s position, Applicants defer substantive rebuttal until the conflicting claims of the above-identified co-pending applications have been allowed.

#### CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee

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occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,  
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